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TENT COOPERATION TRE Y

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
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Washington, D.C.20231
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in its capacity as elected Office

Date of mailing (day/month/year)

24 February 2000 (24.02.00)

International application No.

PCT/GB99/02158

Applicant's or agent's file reference

IS/CP5787593

International filing date (day/month/year)

06 July 1999 (06.07.99)

Priority date (day/month/year)

06 July 1998 (06.07.98)

Applicant

KELLENBERGER, Johannes, Laurenz et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

02 February 2000 (02.02.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia RANAIVOJAONA

Telephone No.: (41-22) 338.83.38

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IS/CP5787593	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB99/02158	International filing date (day/month/year) 06/07/1999	Priority date (day/month/year) 06/07/1998
International Patent Classification (IPC) or national classification and IPC C12N15/52		
Applicant BIOTICA TECHNOLOGY LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 02/02/2000	Date of completion of this report 02.11.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer A. M. Merlos Telephone No. +49 89 2399 8559 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02158

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

Description, pages:

1-57 as originally filed

Claims, No.:

1-27 as originally filed

Drawings, sheets:

1/13-13/13 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02158

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	21-27
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. The preliminary examination report has also been drawn on basis of SEQ ID Nos 1-61.

V Novelty and Inventive Step

2. In view of document EP-0490474, which discloses a fermentative process for production of avermectin B1 substantially free of avermectin B2 (see example), claims 23 to 27 are not considered to refer to novel and inventive matter in the sense of Art. 33(2), (3) PCT.
Furthermore, document US 4,199,569 describes production of 22,23-dihydro C-076 B1(ivermectin, 22,23-dihydroavermectin B1), (examples 6, 7 and 8) and is therefore considered detrimental to the subject-matter of claims 21 and 22 (Art. 33(2), (3) PCT).
3. With respect to the available prior art, claims 1-20 appear to refer to novel subject-matter, in particular because they involve a polylinker comprising multiple restriction sites. This feature was nowhere disclosed in the documents cited. It is however doubted whether it contributes an inventive aspect to the invention. The production of polyketides via replacment of domains involved in reduction in respective polyketide synthases is already known in the art (see e.g. Kao,C.M. et al.J. of the Am. Chem. Assoc., vol. 119, no. 46, 1997, 11339-340, or Mc Daniel,R. et al., J. of the Am. Chem. Soc., vol. 119, no. 18, 1997, 4309-4310). The technical contribution provided by the invention is the use of a polylinker comprising multiple restriction sites to facilitate swapping of domains and/or modules. The use of polylinkers for the purpose of facilitating cloning procedures is however a well-known and commonly applied strategy which does not require particular inventive skill. Moreover, the polylinker was placed in the AT-ACP boundaries, already mutated in Bedford et al. to create resctriction sites PstI and XbaI (see Bedford et al., Chem. and Biol., 1996, vol. 3, no. 10, pages 827-831, paragraph "Significance", Figure 3).
The IPEA is therefore of the opinion that the subject-matter of claims 1-20 is not based on inventive activity according to Art. 33(3) PCT.

VIII Clarity

4. The expressions "loading module" and "extension module" appear unclear because they are not commonly used in the art.

In absence of a defined number of restriction sites contained in the polylinker, claim 4 which refers inter alia to a polylinker wherein "at least some of the restriction sites are absent" does not make sense. It is noted that documents cited in 2.) above may be considered to disclose such nucleic acids insofar as they comprise two restriction sites.

Claim 27 appears to correspond to claim 26.

VI Certain documents cited

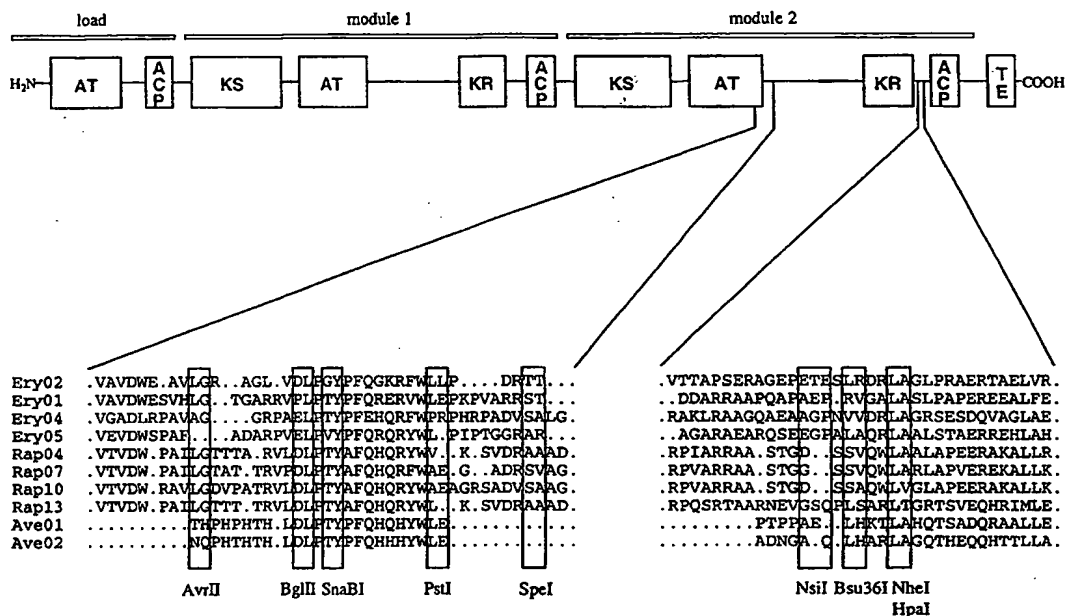
5. Intervening document WO 00/00618 filed on 29.06.99, claiming a priority of 29.06.98 and being published on 06.01.2000 may become relevant for the assessment of novelty when the application enters the european phase.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/52, 15/62, 9/02, 9/04, 9/10, 9/88, C12P 17/06, 19/62, C07K 19/00		A3	(11) International Publication Number: WO 00/01827
			(43) International Publication Date: 13 January 2000 (13.01.00)
(21) International Application Number: PCT/GB99/02158		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 6 July 1999 (06.07.99)			
(30) Priority Data: 9814622.8 6 July 1998 (06.07.98) GB			
(71) Applicants (for all designated States except US): BIOTICA TECHNOLOGY LIMITED [GB/GB]; 112 Hills Road, Cambridge CB2 1PH (GB). PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): KELLENBERGER, Johannes, Laurenz [CH/CH]; Hohlweg 7, CH-4125 Riehen (CH). LEADLAY, Peter, Francis [GB/GB]; 17 Clarendon Road, Cambridge CB2 2BH (GB). STAUNTON, James [GB/GB]; 29 Porson Road, Cambridge CB2 2ET (GB). STUTZMAN-ENGWALL, Kim, Jonelle [US/US]; 547 Boston Post Road, East Lyme, CT 06333 (US). McARTHUR, Hamish, Alastair, Irvine [GB/US]; 19 Pheasant Run Drive, Gales Ferry, CT 06335 (US).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(74) Agents: STUART, Ian et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).		(88) Date of publication of the international search report: 27 April 2000 (27.04.00)	

(54) Title: POLYKETIDES, THEIR PREPARATION, AND MATERIALS FOR USE THEREIN



(57) Abstract

Nucleic acid molecules encoding at least part of a Type I polyketide synthase, and having a polylinker with multiple restriction enzyme sites in place of one or more PKS genes encoding enzymes associated with reduction, optionally further including nucleic acid incorporated into the polylinker, the further nucleic acid encoding one or more reductive enzymes; plasmids incorporating such nucleic acids; host cells transfected with such plasmids; methods relating thereto.

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DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 99/02158

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/52 C12N15/62 C12N9/02 C12N9/04 C12N9/10
C12N9/88 C12P17/06 C12P19/62 C07K19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C12P C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KAO C M ET AL.: "Gain of function mutagenesis of the erythromycin polyketide synthase. 2. Engineered biosynthesis of an eight-membered ring tetraketide lactone" JOURNAL OF THE AMERICAN CHEMICAL ASSOCIATION, vol. 119, no. 46, 19 November 1997 (1997-11-19), pages 11339-11340, XP002131162 cited in the application the whole document</p> <p style="text-align: center;">— — — — — — / —</p>	1-16, 18-20, 24

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

25 February 2000

Date of mailing of the international search report

13/03/2000

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3018

Authorized officer

van de Kamp, M

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 99/02158

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MCDANIEL R ET AL.: "Gain-of-Function Mutagenesis of a Modular Polyketide Synthase" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 119, no. 18, 7 May 1997 (1997-05-07), pages 4309-4310, XP002130959 the whole document	1-11, 13-16, 18-20,24
X	US 4 199 569 A (CHABALA JOHN C ET AL) 22 April 1980 (1980-04-22) examples 6-8,11 claims 1,6,8,10	21,22
X	EP 0 490 474 A (MERCK & CO INC) 17 June 1992 (1992-06-17) example 8 claim 9	23-27
A	KHOSLA C: "Harnessing the biosynthetic potential of modular polyketide synthases" CHEMICAL REVIEWS, vol. 97, no. 7, 1997, pages 2577-2590, XP002130646 the whole document page 2588, paragraph D	1-20,24
A	BEDFORD D ET AL: "A functional chimeric modular polyketide synthase generated via domain replacement." CHEMISTRY AND BIOLOGY, vol. 3, no. 10, October 1996 (1996-10), pages 827-831, XP000884261 cited in the application abstract figure 3 page 829, right-hand column, line 22 -page 830, left-hand column, line 17	1-16, 18-20,24
A	WO 98 01546 A (CORTES JESUS ;LEADLAY PETER F (GB); STAUNTON JAMES (GB); BIOTICA T) 15 January 1998 (1998-01-15) page 8, line 13 -page 9, line 29 page 131, line 4-32	1-8
A	EP 0 391 594 A (MERCK & CO INC) 10 October 1990 (1990-10-10) page 12, line 20-40 claims 12,22	20-27
E,L	WO 00 00618 A (LEADLAY PETER FRANCIS ;CORTES JESUS (GB); STAUNTON JAMES (GB); BIO) 6 January 2000 (2000-01-06) L: priority examples 21,11,25	1-11, 13-20,24

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Patent Application No.

PCT/GB 99/02158

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AT 366690 B	26-04-1982
		AT 711378 A	15-09-1981
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		EP 0910633 A	28-04-1999
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		GB 2331518 A	26-05-1999
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		PL 331285 A	05-07-1999
		AU 7666198 A	30-12-1998
		WO 9854308 A	03-12-1998
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		AT 129286 T	15-11-1995
		AU 626398 B	30-07-1992

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02158

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0391594 A		AU 5244590 A	04-10-1990
		CA 2013524 A	30-09-1990
		DE 69023036 D	23-11-1995
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		NZ 233116 A	27-09-1993
		ZA 9002476 A	28-12-1990
WO 0000618 A	06-01-2000	WO 0000500 A	06-01-2000

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference IS/CP5787593	FOR FURTHER ACTION		see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/GB 99/ 02158	International filing date (day/month/year) 06/07/1999	(Earliest) Priority Date (day/month/year) 06/07/1998	
Applicant BIOTICA TECHNOLOGY LIMITED et al.			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1
☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No.

T/GB 99/02158

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/52 C12N15/62 C12N9/02 C12N9/04 C12N9/10
C12N9/88 C12P17/06 C12P19/62 C07K19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C12P C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KAO C M ET AL.: "Gain of function mutagenesis of the erythromycin polyketide synthase. 2. Engineered biosynthesis of an eight-membered ring tetraketide lactone" JOURNAL OF THE AMERICAN CHEMICAL ASSOCIATION, vol. 119, no. 46, 19 November 1997 (1997-11-19), pages 11339-11340, XP002131162 cited in the application the whole document</p> <p style="text-align: center;">--- -/--</p>	1-16, 18-20, 24



Further documents are listed in the continuation of box C.



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* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 February 2000

Date of mailing of the international search report

13/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

Authorized officer

van de Kamp, M

INTERNATIONAL SEARCH REPORT

International Application No

T/GB 99/02158

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MCDANIEL R ET AL.: "Gain-of-Function Mutagenesis of a Modular Polyketide Synthase" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 119, no. 18, 7 May 1997 (1997-05-07), pages 4309-4310, XP002130959 the whole document	1-11, 13-16, 18-20,24
X	US 4 199 569 A (CHABALA JOHN C ET AL) 22 April 1980 (1980-04-22) examples 6-8,11 claims 1,6,8,10	21,22
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